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A BRIEF ORIGINAL CONTRIBUTION

Blind Assignment of Exposure Does Not Always Prevent Differential Misclassification

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The authors argue that one can never be certain whether an exposure variable which is measured with error is subject to differential misclassification in either a case-control study or a cohort study. They present hypothetic examples that demonstrate that even when misclassification is nondifferential in a 2 × 3 table, the observed odds ratios in the 2 × 2 table created by collapsing over two exposure levels can be either in the opposite direction from or more extreme than the odds ratio that would be obtained if exposures were classified correctly. The anomalies are explained by the observation that the 2 × 2 tables exhibit differential misclassification. In general, collapsing over categories which have different risks of disease and different probabilities of exposure misclassification can induce differential misclassification and even nonconservative estimates of relative risk. Collapsing of exposure levels can occur in the analysis or at the exposure assessment stage. Since indistinguishable categories can be collapsed implicitly, blind assessment of exposure, i.e., assignment without knowledge of disease status, does not guarantee that misclassification is nondifferential. *Am J Epidemiol* 1991;134:433–7.

bias (epidemiology); case-control studies; cohort studies; epidemiologic methods; misclassification, nondifferential

Errors in measurement of exposure are often unavoidable in epidemiologic studies. Nonetheless, epidemiologists have been comforted by the thought that blind assignment of exposure, i.e., assignment of exposure without knowledge of disease status, guarantees that misclassification is always nondifferential. Hence, the estimate of relative risk will be more conservative—suggesting the same direction of effect, but closer to the null—than what would be obtained if exposure had been determined without error. Thus, for example, in any prospective study in which exposure is ascertained before disease status, it is usually assumed that misclassification is nondifferential. Similarly, in a case-control study, care is taken to make sure that an interviewer or assessor of exposure is blinded to the disease status of the subject. However, we argue below that blindness of exposure ascertainment assures neither nondifferential misclassification nor a conservative estimate of relative risk.

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DIFFERENTIAL MISCLASSIFICATION DESPITE BLIND EXPOSURE ASSESSMENT

We present here two simple examples to show that misclassification can be differential and can yield estimates of relative risk that are nonconservative despite blind as-

TABLE 1. Example of nondifferential misclassification of exposure resulting in a reversal of the direction of the association after exposure status is collapsed

	True exposure			
	None	Low	High	Low or high
No. of cases	50	350	600	950
No. of controls	100	700	200	900
Odds ratio	1.00	1.00	6.00	2.11
	Misclassified* exposure			
	None	Low	High	Low or high
No. of cases	170	350	480	830
No. of controls	140	700	160	860
Odds ratio	1.00	0.41	2.47	0.79

* In this example, 20 percent of the high-exposure cases and controls have been misclassified as nonexposed.

sessment of exposure. The top half of table 1 displays data from a 2 × 3 table that would be obtained if the true exposures of all subjects were observed in a hypothetic case-control study. The bottom half of the table presents the outcome of a possible scenario in which 20 percent of all subjects in the high-exposure group are misclassified as unexposed while everyone else is correctly classified. Assuming that the low- and high-exposure categories are then collapsed into an any-exposure category, the misclassified odds ratio of 0.79 differs markedly from the true odds ratio of 2.11. In fact, a protective effect is suggested, whereas the exposure is actually hazardous. Note that this example also demonstrates the phenomenon we discussed in our earlier report (1): The misclassified odds ratio for the low-exposure category indicates a protective association of 0.41 instead of the true 1.00.

The example in table 2 shows that bias away from the null can also occur. Assuming that 20 percent of the cases and controls in the low-exposure category are misclassified as nonexposed, the misclassified odds ratio of 2.19 in the collapsed table indicates a stronger association than the true odds ratio of 2.00.

Thus, despite the fact that the misclassification of the true exposure distribution in the original 2 × 3 table was nondifferential, the odds ratio estimate in the collapsed 2 × 2 table is not always conservative or even in the same direction as the true value. This may seem surprising, since nondifferential misclassification of exposure in a 2 × 2 table results in a conservative estimate of relative risk (except in the extreme situation where the sum of the probabilities of misclassification for truly exposed and truly unexposed subjects is greater than 1). Our earlier report showing that nondifferential misclassification can result in conservative bias (1) applies only to 2 × K tables, with $K > 2$. These anomalies can be explained by noting that the misclassification is differential in the collapsed table. Consider the matrices of misclassification probabilities, P_{ij} = Pr(observing exposure i|true exposure level j). The matrices for the first example are presented in table 3. The misclassification matrices are the same for cases and controls in the 2 × 3 table; however, in the collapsed 2 × 2 table, the matrices are different: The probability of observing any exposure for an exposed case is 0.87 = ((350 × 1.0) + (600 × 0.8))/950, which is less than the corresponding probability of 0.96 = ((700 × 1.0) + (200 × 0.8))/900 for an exposed control. In the second example, these probabilities are 0.92 and 0.84 for cases and controls, respectively.

The misclassification probability for the any-exposure category is a mixture of the two probabilities for the low- and high-exposure categories. In the examples, the weights of the mixture differ by disease sta-

TABLE 2. Example of nondifferential misclassification of exposure resulting in a stronger association than the actual one after exposure status is collapsed

	True exposure			
	None	Low	High	Low or high
No. of cases	500	200	300	500
No. of controls	700	280	70	350
Odds ratio	1.00	1.00	6.00	2.00
	Misclassified* exposure			
	None	Low	High	Low or high
No. of cases	540	160	300	460
No. of controls	756	224	70	294
Odds ratio	1.00	1.00	6.00	2.19

* In this example, 20 percent of the low-exposure cases and controls have been misclassified as nonexposed.

TABLE 3. Misclassification matrices with conditional probabilities for cases and controls before and after collapsing in table 1

True exposure	Observed exposure before collapsing					
	Cases			Controls		
	None	Low	High	None	Low	High
None	1.00	0	0	1.00	0	0
Low	0	1.00	0	0	1.00	0
High	0.20	0	0.80	0.20	0	0.80
	Observed exposure after collapsing					
	Cases			Controls		
	None	Low or high		None	Low or high	
None	1.00	0		1.00	0	
Low or high	0.13	0.87		0.04	0.96	

tus. In table 1, the weights for the low-exposure category are markedly different: 0.37 = 350/950 for the cases and 0.78 = 700/900 for the controls. These weights will be different whenever there is a difference in the odds ratio between the low- and high-exposure categories. In general, nondifferential misclassification will be preserved only if either the odds ratios of the collapsed categories (low and high in our example) are the same or the misclassification matrices for the collapsed categories are equal (see the Appendix). Similar differential misclassification can be expected when an exposure which is measured on a continuous scale and is monotonically related to risk of disease is assigned to discrete categories; this can be seen by applying the results from the Appendix with each possible exposure considered a distinct category.

DISCUSSION

The numbers in our two hypothetic examples are typical of what might be found in case-control studies. Multiplying the numbers of controls by 100 and dividing the numbers of cases by 10 would make the tables look like they came from a cohort study. However, neither the odds ratios nor the misclassification matrices would be affected, and the presence of differential misclassification leading to bias which was not conservative would remain.

We have shown that differential misclassification can occur whenever two or more categories which are heterogeneous in both risk and misclassification probabilities are collapsed. Differential misclassification can be induced in the analysis stage by collapsing over two distinguishable categories. For example, iris color in a study of eye melanoma is an exposure variable for which collapsing is likely to be considered. Kliman et al. (2) categorized irises into light color (blue, gray, or green) and dark color (brown or hazel) groups. Both categories were created by collapsing over categories with possibly heterogeneous risks and heterogeneous probabilities of misclassification into the other group, and therefore could have created differential misclassification. While we do not know what the best strategy would be in this situation, we do suggest that comparisons be made between pairs of individual colors, i.e., before any collapsing, in a preliminary stage of the analysis.

Collapsing of categories is not always explicit. Misclassification can be differential when indistinguishable exposure categories are collapsed implicitly at the assessment stage. For example, workers with the same "job" in two different factories may perform their tasks with subtly different procedures entailing different risk. If the quality of the work history records is better in one of the factories, differential misclassification could be induced.

Thus, a latent variable which is related to risk of disease and to probability of exposure misclassification can induce differential misclassification. This differs from confounding, the extent of which depends on the relation of the latent variable to exposure itself. Unlike the confounding problem, we know, at least in theory, how to alleviate the misclassification problem—improve the accuracy of exposure assessment.

The extent of the distortions in the odds ratio depends on the misclassification matrix, the distribution of exposure, and the true odds ratios. Our examples were selected to demonstrate the possibility of a bias in the odds ratio that is not conservative despite blind assessment of exposure. In particular, our first example is characterized by rela-

tively small numbers of subjects in the baseline exposure category. Further work is needed to assess the impact of the phenomenon in practical epidemiologic applications.

In a related paper (3), we have shown that similar distortions can also arise from misclassification of outcome in a clinical trial, even when the diagnoses were made in a masked or blinded fashion. This phenomenon could affect cohort and case-control studies with blinded diagnosis when the disease being studied is defined as one of several component events. For example, the various histologic types could be considered component events for the outcome "lung cancer." If exposure is dichotomous, exaggeration or reversal of effects can occur when 1) the presence of exposure increases the risk for at least one component condition and decreases the risk for another one and 2) the probabilities of misclassification vary across component conditions (3).

We used to think that blind exposure ascertainment necessarily implied nondifferential misclassification. We have shown that this belief is a misconception and that even nonconservative estimates of relative risk can be obtained despite blind exposure assignment in a case-control study, or even in a cohort study where exposure is obtained before the disease process has begun. This should also serve as a warning that collapsing into discrete categories from a larger number of discrete categories or from a continuous variable should be undertaken cautiously. These considerations underscore the importance of accurate exposure and disease assessment for cohort and case-control studies.

REFERENCES

1. Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol 1990;132:746–8.
2. Kliman GH, Augsburger JJ, Shields MD. Association between iris color and iris melanocytic lesions. Am J Ophthalmol 1985;100:547–8.
3. Wacholder S, Lubin JH, Dosemeci M, et al. Bias despite masked assessment of clinical outcomes when an outcome is defined as one of several component events. Controlled Clin Trials 1991; 12:457–61.

APPENDIX

To see how the collapse of cells within a table with multiple levels of exposure into a table with fewer exposure categories may induce differential misclassification, suppose there are $J + 1$ exposure categories with observed $x_0, x_1, \ldots, x_J$ counts for cases and $y_0, y_1, \ldots, y_J$ counts for controls. If levels $1, \ldots, J$ are collapsed into a single exposed category with level 0 being nonexposed, the observed counts are x_0 and $\tilde{x} = x_1 + \ldots + x_J$ for cases and y_0 and $\tilde{y} = y_1 + \ldots + y_J$ for controls. The odds ratio for the *exposed* is

$$\tilde{\psi} = \frac{\tilde{x}y_0}{x_0\tilde{y}}.$$

Misclassification probabilities for cases and controls can be derived for the collapsed table. Suppose i and j indices refer to the observed and true levels of exposure, respectively. In the full $2 \times (J + 1)$ table, let $P(i|j, d)$ be the probability of observing exposure level i for outcome type d when the true exposure is level j, where d indicates disease status. Nondifferential misclassification implies $P(i|j, d = 1) = P(i|j, d = 0) = P(i|j)$. Consider $Q(i|j, d)$, the misclassification probability in the collapsed table.

1) For $i = 0$ and $j = 0$, the misclassification probabilities are nondifferential, since

$$Q(i = 0|j = 0, d) = P(i = 0|j = 0).$$

For $i = 1$ and $j = 0$, the misclassification probabilities in the collapsed table are nondifferential, since they are the sum of the original (nondifferential) misclassification probabilities,

$$Q(i = 1|j = 0, d) = P(i \geq 1|j = 0, d) = \sum_{k=1}^{J} P(i = k|j = 0).$$

2) For general i and $j = 1$, the misclassification probabilities are a weighted sum of the

original nondifferential misclassification probabilities, namely,

$$Q(i|j = 1, d) = P(i|j \geq 1, d)$$
$$= \frac{\sum_{k=1}^{J} P(i, j = k|d)}{\sum_{l=1}^{J} P(j = l|d)}$$
$$= \sum_{k=1}^{J} w_k(d)P(i|j = k),$$

where the weights are given by

$$w_k(d) = \frac{P(j = k|d)}{\sum_{k=1}^{J} P(j = k|d)}$$
$$= \frac{[\Psi_k]^d P(j = k|d = 0)}{\sum_{l=1}^{J} [\Psi_l]^d P(j = l|d = 0)},$$

where Ψ_k is the true odds ratio for level k. The weights depend on disease status, and hence the misclassification probabilities, Q, can be differential.

Condition 1 indicates that misclassification remains nondifferential for exposure levels not involved in the collapsing.

Condition 2 indicates that the degree and direction of difference in the differential misclassification probabilities for cases and controls depend on the values of Ψ_k and of $P(j = k|d)$. Q will *not* differ for cases and controls when the Ψ_k for the cells which are being collapsed are the same or when the misclassification probabilities $P(i|j = k)$ for $k \geq 1$ are equal.